MTF Formulary Management for Diabetes Drugs

Defense Health Agency Pharmacy Operations Division
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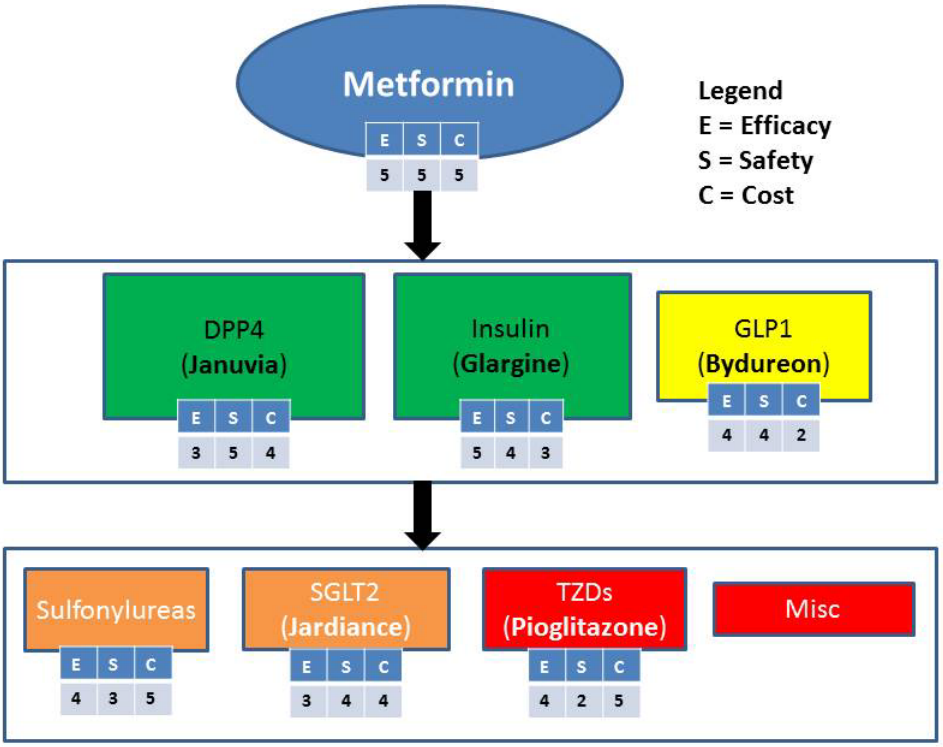
Bottom Line

- **Step therapy exists in most diabetes classes. Patients must first try metformin or a sulfonylurea before use of non-insulin diabetes drugs.**
- **Preferred agents exist within the DPP-4, SGLT2, and GLP1RA classes (i.e., sitagliptin, empagliflozin, exenatide once weekly, and albiglutide).**
- **Prior authorization criteria apply to U-300 insulin, insulin degludec, and inhaled insulin.**



If A1c target is not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order of medications represents a suggested hierarchy of usage; however, choice of drug is dependent on a variety of patient-specific factors). In certain clinical situations, a 2-drug regimen may be appropriate at initiation.

Efficacy: The Efficacy measure is the extent to which an intervention is helpful in reducing A1C, improving outcomes, of a medical condition. The scale used to measure efficacy is:
5 (Highly effective): Achieves A1C reduction >1.5%
4 (Very effective): Achieves A1C reduction >1.0%
3 (Moderately effective): Achieves A1C reduction >0.5%
2 (Minimally effective): Modest, no, or unknown impact on A1C
1 (Not effective): Provides no benefit

Safety: Safety refers to the assessment of the relative likelihood of side effects from an intervention with fewer side effects being scored highly. The scale used to measure safety is:
5 (Usually no meaningful adverse effects): Uncommon or minimal side effects
4 (Infrequent adverse effects): Rare significant side effects or low-grade side effects only
3 (Occasional adverse effects): Mild side effects such as edema that interfere with ADLs is common.
2 (Frequent adverse effects): Significant side effects often occur, such as hypoglycemia. Life threatening issues are uncommon.
1 (Severe adverse effects): Usually severe, significant toxicities or life threatening/fatal toxicity often observed.

Cost: Affordability refers to drug costs per month within the DoD.
5 Very inexpensive $5 – $50
4 Inexpensive $50 – $100
3 Moderately expensive $100 – $200
2 Expensive $200 – $400
1 Very expensive > $400

Uniform Formulary Decisions

BCF drugs – MTFs must have on formulary		
• Metformin IR 500 mg, 850 mg, 1000 mg • Metformin XR 500 mg, 750 mg		• Fortamet (500 mg, 1000 mg) • Glumetza (500 mg, 1000 mg)
• Glargine (Lantus) Solostar Prefilled Pens and vial • Novolin N Vial • Humulin N KwikPen and Vial	• Detemir (Levemir) vial • Glargine U-300 (Toujeo)*	• Detemir (Levemir) FlexTouch Pen • Insulin degludec (Tresiba)
Step-Preferred • Sitagliptin (Januvia) • Sitagliptin/metformin (Janumet) • Sitagliptin/metformin ER (Janumet XR)	**Non Step-Preferred** • Linagliptin (Tradjenta) • Linagliptin/metformin IR (Jentadueto) • Linagliptin/metformin XR (Jentadueto XR)	**Non Step-Preferred** • Alogliptin (Nesina) • Alogliptin/metformin (Kazano) • Alogliptin/pioglitazone (Oseni) • Saxagliptin (Onglyza) • Saxagliptin/metformin ER (Kombiglyze XR)
Step-Preferred • Exenatide Q Week (Bydureon)	**Step-Preferred** • Albiglutide (Tanzeum)	**Non Step-Preferred** • Exenatide BID (Byetta) • Liraglutide (Victoza) • Dulaglutide (Trulicity)
	Step-Preferred • Empagliflozin (Jardiance) • Empagliflozin/metformin (Synjardy) • Empagliflozin/linagliptin (Glyxambi)	**Non Step-Preferred** • Canagliflozin (Invokana) • Canagliflozin/metformin (Invokamet) • Canagliflozin/metformin XR (Invokamet XR) • Dapagliflozin (Farxiga) • Dapagliflozin/metformin XR (Xigduo XR)
• Glimepiride • Glipizide, Glipizide ER • Glyburide, Glyburide micronized		
	• Pioglitazone • Pioglitazone/glimepiride • Pioglitazone/metformin • Pioglitazone/metformin XR	• Rosiglitazone • Rosiglitazone/metformin • Rosiglitazone/glimepiride
• Novolog Vial and FlexPen	• Humalog Vial and KwikPen • Apidra Vial and Solostar Pen	• Afrezza (inhaled insulin)*
Step-Preferred • Precision Xtra test strips • FreeStyle Lite test strips	**Meglitinides** • Nateglinide • Repaglinide **AGIs** • Acarbose • Miglitol **Amylin Agonist** • Pramlintide (Symlin) **Insulins** • Humulin R, Novolin R • NPH Insulin	**Dopamine agonist** • Bromocriptine (Cycloset)

Formulary Management Issues

1. A patient-centered approach to therapy is recommended using shared decision-making with the patient. Lifestyle interventions including diet, exercise, and behavioral modifications are foundations for successful management of patients with diabetes.
2. Consider efficacy, safety, and cost combined with a patient-centered approach when choosing agents.
3. Metformin remains the first-line treatment in all type 2 diabetes mellitus (T2DM) patients unless contraindications exist.

Biguanides: (Metformin)

- Metformin is the preferred first-line agent providing a 1%–2% decrease in A1c.
- Metformin is not associated with weight gain, has a low risk for hypoglycemia, and is the most cost-effective agent.
- Titration to the maximally-effective dose helps to mitigate potential adverse GI effects.
- Renal monitoring is recommended and metformin should be avoided in patients with factors predisposing to lactic acidosis.

DPP-4 Inhibitors: Sitagliptin (Januvia)

- DPP4s have intermediate efficacy and a low risk of hypoglycemia. They are weight neutral, have few common side effects, and represent an intermediate cost.
- Cardiovascular (CV) outcomes trials have been completed with three of the four drugs showing no difference between active drug and placebo in terms of effect on cardiovascular outcomes.

GLP-1 Receptor Agonists: Exenatide Once Weekly (Bydureon) and Albiglutide (Tanzeum)

- GLP1RAs have high efficacy, typically lowering A1c greater than 1%. The results of seven head-to-head trials do not show clinically significant differences between GLP1RAs in effects on glycemic control.
- Trulicity, Tanzeum, and Bydureon have the advantage of once weekly dosing, Victoza is dosed once daily, and Byetta is dosed twice daily.
- Benefits of GLP1RAs include a low risk of hypoglycemia and weight loss, while GI side effects and a significant cost may limit their use.
- Three out of six GLP1RA CV outcomes trials have been completed to date. The LEADER trial with liraglutide and the SUSTAIN 6 trial with once weekly injectable semaglutide showed a decrease in major adverse cardiovascular events. Semaglutide has not been approved by the FDA. The ELIXA trial with lixisenatide showed it was no better and no worse than placebo. EXSCEL (exenatide once weekly), HARMONY-OUTCOMES (albiglutide), and REWIND (dulaglutide) are still ongoing.

SGLT2 Inhibitors

- In general, the SGLT2 inhibitors have intermediate efficacy lowering A1c than 1% when used as monotherapy. There are no head-to-head trials between any of the SGLT2 inhibitors.
- Benefits of SGLT2 inhibitors include a low risk of hypoglycemia, slight decrease in weight (reduction on average of 1.8 kg), blood pressure, HDL cholesterol, and triglycerides. Disadvantages include female genital mycotic infections, urinary tract infections, increases in LDL cholesterol and an intermediate cost.
- The SGLT2 inhibitors should be avoided in renal impairment. There is a recent FDA safety alert for the class for ketoacidosis. Patients with a history of bladder cancer should avoid dapagliflozin.
- The cardiovascular (CV) safety profile of the SGLT2 inhibitors as a class remains unclear. To date, only one CV trial has been completed. The EMPA-REG OUTCOME trial with empagliflozin showed a 2.2% absolute risk reduction in death from CV causes; however, limitations to the trial exist and results should not be extrapolated to the entire class. The CANVAS trial (canagliflozin) and DECLARE-TIMI 58 (dapagliflozin) are still ongoing.

Sulfonylureas (SU)

- While sulfonylureas achieve a 1%–2% A1c reduction from baseline, they also present a moderate risk of hypoglycemia that requires close monitoring.
- Lifestyle changes can help mitigate the potential side effect of 2-3 kg weight gain.
- Although historically favored after metformin as an oral option due to cost, individual patients may benefit from alternative options.

TZDs: Pioglitazone (Actos)

- Cost and side effects make TZDs less appealing as an initial therapy.
- Pioglitazone reduces HbA1C 1%–1.5% from baseline, with a low risk of hypoglycemia.
- Side effects of concern include edema, heart failure, and weight gain.
- While the FDA eliminated a Risk Evaluation and Management Strategy (REMS) for rosiglitazone-containing medicines in Dec 2015, rosiglitazone and its fixed-dose combinations remain nonformulary.

Insulin

- Insulin may be the most efficacious agent available, for some individuals. Given the natural progression of the disease, most patients will require additional interventions over time.
- Insulin can be considered as early as the first choice after metformin and in patients with an A1c > 9%–9.5% at the start of therapy.
- Differences between insulin regimens are typically minimal. This assumes adequate titration of insulin doses.
- Basal insulin offers potentially greater patient satisfaction and less risk of hypoglycemia when compared to other insulins.
- Compared to other classes, there may be more hypoglycemia and weight gain when using insulin.
- Prandial insulin (mealtime insulin) should be used to help manage glucose excursions related to meals (i.e., insulin lispro, glulisine, and aspart).
- Recent trials have shown that intensive glucose control (i.e., targeting A1c of 6) may worsen clinical outcomes. The United Kingdom Prospective Diabetes Study (UKPDS) showed a 15% reduction in myocardial infarction and a 13% reduction in death among people with new-onset T2DM compared to placebo.
- Costs vary but the newer insulins (U-300 and degludec) are more costly. Expect a biosimilar insulin glargine near the end of 2016.

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- DoD P&T Committee minutes: http://www.health.mil/PandT
- Current/future drug classes under review by the DoD P&T Committee: http://www.health.mil/PandT (scroll down to DoD P&T Committee Meeting Schedule)
- TRICARE Formulary Search Tool: http://www.health.mil/formulary
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: http://www.health.mil/DoDPTResources.
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil